

ETHICAL ASPECTS AND SOCIOLOGICAL IMPLICATIONS OF ORGAN TRANSPLANTATION AS A THERAPEUTIC PROCEDURE

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Transplantation, as such, is not controversial, nor does the concept of transferring living tissue from one person to another involve any ethical problems. Transfusion of blood, which of course includes living cells, and transplantation of corneal tissue in eye clinics are simply routine procedures today.

However, before a treatment can be considered therapeutic, it must pass through a series of clinical trials. The ethical problems presented by transplantation of the heart, for example, are similar to those involved in any experimental treatment, and the same general rules apply: the patient must be informed and willing, the procedure must not subject him to a hazard much greater than already exists in his disease, the preliminary work must be thorough enough to give maximum chance of success, and the trial must be well-designed so that future patients will benefit from the experience. If the experience with an experimental procedure is favorable, the procedure will gradually pass from experimental status and become a medical routine.

Transplantation of the kidney is not yet routine, but is approaching the therapeutic stage. Thanks to the careful documentation provided by investigators in this field, the probable outcome with existing techniques can be predicted. A team of experienced physicians can prescribe transplantation as a treatment rather than as an experiment for a patient with renal disease. If this is done, the patient's outcome will add only one more datum to a large list. It will be a treatment result, not an experimental finding.

On the other hand, the techniques of tissue matching and control of rejection continue to evolve. The hope is that with greater understanding of these complexities transplantation might become more consistently successful, and it might even become possible to use kidneys from other species. To the extent that new techniques are being tried, renal transplantation continues in experimental status.

Transplantations of heart, liver, lungs, pancreas, and bone marrow are much more difficult to evaluate. An important beginning in critique was made by the Board of Medicine of the National Academy of Sciences shortly after the first cardiac transplant. It clearly identified this as an experimental procedure, recognized that the main problems would be immunological rather than surgical, and emphasized the need for concurrent laboratory studies. The Board also pointed out that "in order to obtain the scientific information necessary for the next phase in this form of organ transplantation, only a relatively small number of careful investigations involving cardiac transplantation need be done at this time." Today, sixteen months and approximately 125 transplants later, it is appropriate to ask how much has been learned from transplantations of the heart and whether the experience to date justifies continuation of this experiment.

Judged as a surgical procedure, cardiac transplantation can be considered

relatively successful. If a newly implanted heart survives for one week, it has proved its viability by almost one million contractions. Approximately 75 per cent of the patients who have received transplants during the past six months have survived for a week or longer. This over-all statistic includes subjects who were *in extremis* at the time of operation and probably could not have survived even a week with conventional treatment. It thus can be said that the technical problems of sustaining life during the temporary absence of a heart, of hooking up the new organ properly, of preventing post-operative shock and other complications have been substantially overcome.

The longer term results, however, are much less encouraging. The majority of recipients have died during the next few months. By six months the survival rate (so far as figures are now available) falls below 20 per cent, and the one-year survival is likely to be significantly lower than that. It cannot be said that this procedure, with present techniques, significantly increases a heart patient's chance of survival, and it may diminish it. Nevertheless, a patient may have interests more important to him than survival; he may prefer a gambler's chance at a cure to a longer life in bed. The statistics, although grim, do not automatically decide the issue from the patient's point of view. The patients are desperate—as you or I might be with terminal disease—but are not exploited.

As to the interests of the public, and especially of the potential candidates for transplant, the important question is how much has been learned from the experience to date. Quite clearly, control of the rejection process has been unsatisfactory. Although it was hoped at the onset that the heart would be less antigenic than the kidney, it now appears that the reverse may be true. On the other hand, heart transplants have been done under the pressure of emergency, without time for any tests of compatibility, and in no case have been done with close relatives. It also seems theoretically possible that recipients have been sensitized by the foreign blood transfused in the course of heart surgery.

Committees associated with the National Heart Institute, the American College of Surgeons, and other responsible groups have begun to study the accumulated data. It is too early to expect definitive reports from them, but it would be interesting to know at least whether or not these committees are satisfied with the quality of data now being collected, and how many more transplants appear to be needed for the clinical studies.

Derivative to this issue is the question whether there is something unique about the rejection phenomenon in man that requires continuation of the immunological studies in cases of human transplant rather than in experimental animals. It seems to me that studies of cellular recognition and rejection, and of agents to control them, could go forward faster and cheaper in animals. Is the heart-transplant patient, from the scientific point of view, simply a preparation for the study of graft rejection? Is heart transplant in man unique for the study of tissue typing and control of rejection?

A number of serious objections have been raised against transplantation in general, and heart transplants in particular. One is cost. These clinical experiments are extraordinarily expensive. It has been remarked that problems of the cities, of starvation and population control should be given a higher priority.

Although the facilities used in transplantation work cannot go directly to the solution of these problems, the money spent could be spent elsewhere. Are important studies and clinical services, needing the same facilities, being blocked? This question, so far as I can see, is best answered by institutional committees and granting agencies responsible for the allocation of limited funds. Transplantation work, to be funded, must compete with applications from other fields.

In this connection it is important to note that the value of transplantation studies cannot be measured simply by the number of transplants that succeed. In addition to the planned studies, the gain to other, apparently unrelated, fields is sure to be of major importance. For example, the observation that patients on chronic immunosuppressive therapy after renal transplant have a significantly higher incidence of lymphomas and other neoplasms suggests that the cellular rejection process, which is a nuisance in transplantation, may provide a vital defense against the proliferation of abnormal cancer cells. This exciting lead is now being pursued in laboratories directed to the study of neoplasms. The cancer workers undoubtedly are seeking to enhance what the transplanters are trying to suppress.

A better understanding of the immunological processes involved in rejection will clarify the pathology of an assortment of diseases, such as rheumatic diseases, nephritis, and multiple sclerosis, that seem to involve "auto-immune" processes. The immunological studies might even provide a new approach to the problem of arteriosclerosis, which is the major cause of damage to the hearts that have been replaced by transplantation.

The publicity and exaggerated claims associated with some of the heart transplants have disturbed many observers who are otherwise sympathetic to the clinical work. They have expressed fears that the pressures of publicity, prestige, and the like would destroy the delicate balance between research and responsibility to the patient. Some have gone so far as to suggest that additional controls are needed, with enforcement power given to a governmental agency. This, in my opinion, would be a greater evil than the one that it is intended to prevent.

The concerned and articulate leaders of medicine who have written editorials on the subject, convened symposia and committees, sat on review boards for institutions and granting agencies have provided the means to answer their own concern. Effective processes of medical self-regulation do exist. With the leadership of the National Institutes of Health in fostering institutional responsibility, there is now emerging a body of common law, based upon specific decisions, capable of evolving in response to new questions. Speaking as a clinical investigator, I am reassured by this process, and am chilled by the alternative of a rigid code, bureaucratically administered.

Two major ethical problems are encountered in the clinical work. The first, which is unique to transplantation, is the potential conflict of interest between patient and donor, especially in the transplantation of unpaired organs, such as the heart. Obviously, a donor must be dead before his heart is taken. The practical problem is to define the time of death with such precision that the donor is unequivocally dead before removal of his heart, but without so much

delay that the organ has been damaged by postmortem changes. This problem, which seems on first consideration to be insoluble, can be met by defining rigorous criteria of brain death (as distinguished from the later disintegration of organs and cells), and by separating the responsibilities of physicians concerned with the welfare of the prospective donor as a patient from the responsibilities of the transplantation team. The issue of conflicting interests is less acute in renal transplantation, especially when a living adult donor volunteers one of his two normal kidneys and has time to consider his decision—but even in such a case it is difficult to be sure that the donor has not been subjected to undue pressure, especially when he is a uniquely well-matched sibling. What has impressed me on reading the literature on this subject is the universal recognition of the problem as an ethical issue, and the sensitive analysis that it has received from various points of view.

The second ethical problem is that of priorities in allocating services. A preview of this dilemma already exists in the dialysis procedure—an effective but expensive way to sustain life in an individual with no kidney function. The issue here is mainly economic; there are not nearly enough facilities to serve the 10,000 or so individuals who could be kept alive with repeated dialysis but will die without it, and it is too expensive (approximately \$10,000 per year) for the average patient to pay for the treatment himself.

A similar economic problem is emerging in renal transplantation as this procedure passes from the experimental stage (where it receives research subsidies) to the status of effective treatment. The financial support of both dialysis and therapeutic transplantation involve questions of national policy. The principle of publicly supported treatment is accepted for conditions such as narcotics addiction that threaten the public welfare. In my opinion, public support should be extended to chronic diseases in which the only issue is an individual's right to live. It must be recognized, however, that the removal of economic limits does not solve the allocation problem. It merely leads to new limits, which in the case of transplantation are the scarcity of organs and professional services.

The present demand for transplantable hearts and livers already exceeds the supply, although the number awaiting transplant is still relatively low because of currently poor survival statistics. This is almost surely a temporary situation. In the near future the demand for these organs is likely to become overwhelming, since techniques are becoming available for improving the rate of success.

At present, the main difficulty in transplantation of unpaired organs is incompatibility of tissues, due to the use of random, unrelated donors. In such cases the probability of a good tissue match is very low (somewhere between 1/50 and 1/150), and the probability of rejection is correspondingly high. Much better matching could be achieved if society were willing to make a major investment in a centralized registry of potential recipients (already tissue typed), and maintain an efficient system for the immediate typing and delivery of donor tissue.

The logistical problems and expense of such a system would be formidable, perhaps prohibitive, but the point to emphasize here is that the limits in the

near future will be economic rather than scientific. With existing techniques it is possible to keep a heart or liver viable for at least twelve hours after its removal from the body of a donor. During this time a profile of tissue antigens could be determined, a compatible recipient located in a computerized registry, the transplant teams assembled, and the organ delivered by air to the operating room of any hospital within a thousand mile radius. The pool of potential recipients would have to be 200 or more to yield a sufficiently high probability of match, and reports on their status would need to be monitored continuously at the central register since the condition of patients sick enough to be candidates for heart transplant changes from day to day. None of these requirements goes very far beyond existing technology, but with these services the cost of a heart transplant could rise above \$100,000.

Apart from the cost of treatment, serious problems in the allocation of scarce tissue are inevitable in the long run. With approximately 80,000 cardiac deaths per year the demand for hearts will exceed any foreseeable increase in supply. At first, allocation will be determined by the impersonal criterion of tissue matching, but sooner or later control of the rejection process will bridge the incompatibility gap and make the allocation of an organ a matter of life or death to thousands of potential recipients. It is to be hoped that by that time pumps will be available as alternatives to assist or replace failing hearts. The liver, pancreas, and lungs, however, have much more complicated functions. So far as I am aware, no artificial device is in prospect for their replacement.

To summarize: The transplantation of organs in man brings with it a sequence of ethical and social problems. While these procedures are in an experimental stage, the main issues are the concern for the rights of patients and donors who are being subjected to the experiment and the assurance that the trials are well-designed. As the procedures evolve to the status of therapy, cost may become a major issue, but ultimately, when the limiting factor is the supply of organs and treatment is a privilege, the great problem will be allocation.

This survey has brought out four kinds of questions that must be answered by workers in this field:

- (a) What more will be learned from continued transplantation of unmatched hearts and livers? Are more data needed to define the rejection process in man, or should further transplantation be suspended until means are worked out for selection of compatible recipients?
- (b) Is the cost of this work a serious objection? Is the expenditure of money or use of hospital facilities depriving other important projects of needed support?
- (c) Are the existing controls and reviews by committees adequate, or are more explicit controls required?
- (d) The ultimate problem—namely, a fair allocation of organs and services when demand exceeds supply—seems insoluble, but this may be too pessimistic a view. Can we escape the dependence on human tissue sources by the use of grafts from other species and development of artificial organs?